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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/308,080	10/28/1999	FRANK J. GONZALEZ	15280-271100	5674

7590 12/03/2001

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	14

DATE MAILED: 12/03/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/308,080	Applicant(s) GONZALEZ ET AL.	
	Examiner David J. Steadman	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,15-17 and 20-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,15-17 and 20-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-11, 15-17, and 20-28 are pending in the application.

Applicants' cancellation of claims 12-14, 18, and 19, amendment to the specification and claims 1-11 and 15-17, addition of claims 20-28, and receipt of a computer-readable form and paper copy of the sequence listing in Paper No. 12, filed 09/24/01 are acknowledged.

Applicants' arguments in Paper No. 12, filed on 09/24/01, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, Second Paragraph

1. Claims 1-11, 15-17, and 20-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

2. Claims 1-9, 17, 20-23, and 27 are unclear in the recitation of "comprises a G residue at the position indicated as nucleotide 434 of SEQ ID NO:1" in claims 1 (claim 5 dependent therefrom) and 6, "comprises a residue at the position indicated as nucleotide 434 of SEQ ID NO:1" in claims 2 (claims 3, 4, 20, and 21 dependent therefrom) and 7 (claims 8, 9, 22, and 23 dependent therefrom), and "sequence comprising a residue in human dihydropyrimidine dehydrogenase genomic DNA at the position indicated as nucleotide 434 of SEQ ID NO:1" in claims 17 and 27. The claims are unclear as to the scope of polynucleotides encompassed by the claims in regards to the nucleotide sequence and length of the polynucleotide *comprising* nucleotide 434 of SEQ ID NO:1. As written, the claim can be interpreted as meaning any genomic or intronic sequence of human DPD genomic DNA comprising G. It is suggested

that, for example, applicants specifically identify nucleotides of SEQ ID NO:1 that are encompassed by the claim.

3. Claims 4, 5, 9, 16 and 26 are unclear in the recitation of "presence or absence of a G residue". It is not clear whether the "absence of a G residue" is meant to be interpreted as a substitution of a G with another nucleotide or if the G is deleted. It is suggested that applicants clarify the meaning of the claims.

4. Claims 17 (claim 25 dependent therefrom) , 21, 23, 25, 27, and 28 are indefinite in the recitation of "restriction endonuclease which recognizes a sequence" in claims 17 and 27, and "restriction endonuclease recognizes a MaeII cleavage site" in claims 21, 23, 25, and 28. It is unclear as to the meaning of the term "recognizes". It is suggested that applicants replace the term "recognizes" with, for example, "cleaves".

5. Claims 3, 8, 10, 11, 15, 20, 24, and 26 are indefinite in the recitation of "hybridizing" and "binds to" as these terms are unclear absent a statement of the conditions under which hybridization or binding is performed. Nucleic acids which will hybridize or bind under some conditions will not necessarily hybridize or bind under different conditions.

Claim Rejections - 35 USC § 112, First Paragraph

6. The written description rejection of claims 1-4, 8-10, 15-17, 20, 22, 24, 26, and 27 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action.

Claims 1, 2 (claim 20 dependent therefrom), 3, 4, 8 (claim 22 dependent therefrom), 9, 10 (claim 11 dependent therefrom), 15 (claims 16 and 24 dependent therefrom), 17, 26, and 27 are directed to a method of detecting a splicing defect or a method of screening patients for sensitivity to 5-FU by amplifying a genus of human intronic DPD genomic DNAs which comprise nucleotide 434 of SEQ ID NO:1 by using a genus of primers which hybridize to a genus of human DPD genomic sequences within 500 (claims 3 and 8) or 100 nucleotides (claims 20 and 22) of nucleotide 434 of SEQ ID NO:1 or by digesting the amplified DNA with a genus of restriction endonucleases (claims 4 and 9), a composition comprising a genus of PCR primers that bind a genus of human intronic DPD genomic DNAs within 500 (claim 10) or

100 nucleotides (claim 11) of nucleotide 434 of SEQ ID NO:1, a kit comprising a genus of PCR primers that bind to DNA 3' or 5', respectively, of a splice site in a genus of human DPD genomic DNAs for an exon encoding amino acids 581-635, wherein at least one of the primers binds to the sequence within 500 (claim 15) or 100 nucleotides (claim 24) of nucleotide 434 of SEQ ID NO:1, and optionally wherein kit comprises a genus of restriction endonucleases that recognize a genus of sequences comprising nucleotide 434 of SEQ ID NO:1 (claims 17 and 27), and a kit comprising a genus of PCR primers that bind to DNA 3' or 5', respectively, of a splice site in a genus of human DPD genomic DNAs for an exon encoding amino acids 581-635 and instructions for detection of G at nucleotide 434 of SEQ ID NO:1 (claim 26). The specification teaches only a single representative species of human intronic DPD genomic DNAs comprising nucleotide 434 of SEQ ID NO:1, i.e., SEQ ID NO:1, three representative species of PCR primers as encompassed by the claims, i.e., SEQ ID NOs:2-5 and a single representative species of restriction endonucleases, i.e., MaeII. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the description of being a human intronic DPD genomic DNAs comprising nucleotide 434 of SEQ ID NO:1, a PCR primer as encompassed by the claims, or a restriction endonuclease. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants argue that the claimed primers have been fully described in the specification by disclosing structural and functional properties of the genus of claimed primers and methods of use thereof. Applicants argue that by providing the structure of SEQ ID NO:1, one of skill in the art would have sufficient structure to visualize the claimed primers. Applicants arguments are not found persuasive. Applicants have provided only a single species of a human genomic DPD sequence, i.e., SEQ ID NO:1, which is insufficient to describe the entire genus of human genomic DPD sequences. Therefore, because the structural information needed to generate the claimed primers and methods of use thereof is derived from the genomic sequence, applicants have not sufficiently described the genus of human genomic DPD

sequences such that one of skill in the art could visualize the entire genus of primers. Furthermore, applicants have disclosed only a 433 nucleic acid sequence 5′ of position 434 and only a 427 nucleic acid sequence 3′ to position 434 of SEQ ID NO:1. Therefore, it is impossible to visualize all primers that bind *within 500 nucleotides* of nucleotide 434 of SEQ ID NO:1.

7. Claims 4, 9, 17, and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting a splicing defect or a method of screening patients for sensitivity to 5-FU by amplifying human genomic DPD DNA and optionally digesting the amplified DNA with a MaeII restriction endonuclease, or a kit comprising PCR primers and a MaeII restriction enzyme as encompassed by the claims, does not reasonably provide enablement for a method of detecting a splicing defect or a method of screening patients for sensitivity to 5-FU by digesting DNA with *any* restriction endonuclease or a kit comprising PCR primers and *any* restriction endonuclease that recognizes *any* sequence comprising nucleotide 434 of SEQ ID NO: 1 (claims 17 and 27). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 4, 9, 17, and 27 are so broad as to encompass a method of detecting a splicing defect or a method of screening patients for sensitivity to 5-FU by digesting DNA to detect the presence of G at nucleotide 434 of SEQ ID NO:1 with *any* restriction endonuclease or a kit comprising PCR primers and *any* restriction endonuclease that recognizes *any* sequence comprising nucleotide 434 of SEQ ID NO: 1. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of restriction enzymes broadly encompassed by the claims. In this case the disclosure is limited to a method of detecting a splicing defect or a method of screening patients for sensitivity to 5-FU by digesting DNA with MaeII or a kit comprising PCR primers and MaeII as encompassed by the claims.

While restriction digests are known and commonly use in recombinant DNA techniques, it is not routine in the art to screen for multiple restriction endonuclease enzymes in order to detect the presence

of G at nucleotide 434 of SEQ ID NO:1 or recognize a sequence comprising nucleotide 434 of SEQ ID NO: 1, as encompassed by the instant claims. Furthermore, the specification does not support the broad scope of the claims which encompass a method of detecting a splicing defect or a method of screening patients for sensitivity to 5-FU by digesting DNA to detect the presence of G at nucleotide 434 of SEQ ID NO:1 with *any* restriction endonuclease or a kit comprising PCR primers and *any* restriction endonuclease that recognizes *any* sequence comprising nucleotide 434 of SEQ ID NO: 1 because the specification does not establish methods of screening *any* endonuclease to detect the presence of G at nucleotide 434 of SEQ ID NO:1 or recognize *any* sequence comprising nucleotide 434 of SEQ ID NO: 1.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of detecting a splicing defect or a method of screening patients for sensitivity to 5-FU by digesting DNA to detect the presence of G at nucleotide 434 of SEQ ID NO:1 with *any* restriction endonuclease or a kit comprising PCR primers and *any* restriction endonuclease that recognizes *any* sequence comprising nucleotide 434 of SEQ ID NO:1. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants state in the "Remarks" section of Paper No. 12 that "[t]he general use of restriction endonucleases that recognize sites created or destroyed by DPD polymorphisms may be found at page 16, lines 14-29 of the specification". However, the specification discloses the use of only one restriction endonuclease for detecting a DPD polymorphism – MaeII. As stated above, screening for any restriction endonuclease to cleave a sequence comprising nucleotide 434 of SEQ ID NO:1 would result in undue experimentation.

Claim Rejections - 35 USC § 103

8. In view of applicants' amendment to claims 1-3, 5-8, and 16 to recite a specific mutation, e.g., "a G residue at the position indicated as nucleotide 434 of SEQ ID NO:1, wherein substitution of the G residue with an A residue causes a splicing defect", rejection under 35 USC 103(a) is withdrawn. Gonzalez et al. (Trends Pharmacol Sci 16:325-327) suggest sequencing of the intron-exon boundary of a mutant allele of genomic DPD genomic DNA that causes a 165-bp exon to be deleted (page 326-7). Meinsma et al. (DNA Cell Biol 14:1-6; 1995) similarly suggest that the 165-bp deletion of the human DPD mRNA, corresponding to amino acids 581 to 635, is "coincident with a splicing site located in the genomic sequence of the DPYP gene that comprises a 165-bp exon" and that the deletion is due to a mutation that causes incorrect splicing. However, neither Gonzalez et al. or Meinsma et al. teach a G to A mutation at position 1987 (nucleotide 434 of SEQ ID NO:1) of human DPD genomic DNA resulting in deletion of the 165-bp exon.

9. Rejection of claims 10, 11, 15, and 24 under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al. in view of Meinsma et al. is maintained. Claims 10, 11, 15, and 24 are drawn to a composition comprising a PCR primer that binds a human DPD intronic genomic nucleotide sequence within 500 (claim 10) or 100 nucleotides (claim 11) of nucleotide 434 of SEQ ID NO:1, a kit comprising PCR primers that bind either 3' or 5' to a splice site in the human DPD genomic DNA for an exon encoding amino acids 581-635 of human DPD, wherein at least one of the primers binds a human DPD intronic genomic nucleotide sequence within 500 (claim 15) or 100 (claim 24) nucleotides of nucleotide 434 of SEQ ID NO:1.

Applicants argue that the references of Gonzalez et al. and Meinsma et al. are not enabling for the primers of claims 10, 11, 15, and 24 as the references do not teach the intronic nucleotide sequence of human DPD genomic DNA. Applicants' argument is not found persuasive. While neither Gonzalez et al. nor Meinsma et al. specifically disclose the genomic sequence of human DPD, based on the teachings of Gonzalez et al. and Meinsma et al., one of ordinary skill in the art would have known the location of the mutation in the genomic DNA and would have sufficient motivation to create primers to screen for said mutation. Furthermore, one of ordinary skill in the art at the time of the invention would have been able

to use primers designed based on the human DPD cDNA sequence, which was known in the art at the time of the invention as acknowledged by Meinsma et al. (page 2, right column), to sequence between exons using human genomic DNA in order to determine the intronic sequences of human DPD genomic DNA. By comparing the sequences of human DPD genomic and complementary DNA, one of ordinary skill in the art would have identified the intron/exon boundary as described by Gonzalez et al. and Meinsma et al. and would have been motivated to generate the primers as claimed in claims 10, 11, 15, and 24 because of Gonzalez et al. who teach that the intron-exon boundaries of the DPD gene are being determined in order to develop a convenient screening assay for the analysis of cancer patients having DPD gene mutations, and that by determining the intron-exon boundaries of the DPD gene, specific PCR primers could be designed to analyze for mutant DPD genes using a PCR-based screening procedure.

Conclusion

10. No claim is in condition for allowance. All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

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